Patient Persistency with Ocular Prostaglandin Therapy: A Population-Based, Retrospective Study

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ABSTRACT

Background: Open-angle glaucoma affects an estimated 33 million individuals worldwide. An intraocular pressure >21 mm Hg in individuals with no evidence of optic nerve damage is termed *ocular hypertension*, a risk factor for glaucoma that has been estimated to affect as many as 10% of individuals 40 years of age or older.

Objective: The purpose of this research was to assess persistency (time on therapy) with prostaglandin analogues in the treatment of glaucoma or ocular hypertension.

Methods: This population-based, retrospective cohort study used the Protocare Sciences managed care database, which includes prescription and medical claims data from multiple managed care organizations. Patients 20 years of age or older who initiated therapy with latanoprost, bimatoprost, or travoprost (index drugs) between April 2001 and June 2002 were included. Patients were required to be continuously enrolled in the same plan for the 180 days preceding index prescription fill. Follow-up continued through June 30, 2002. Two outcome measures were analyzed: (1) discontinuation of the index prostaglandin and (2) either discontinuation or change in the index prostaglandin regimen. *Changing therapy* was defined as switching to or adding another ocular hypotensive agent. Cox regression models were used to compare rate ratios of discontinuation and discontinuation/change. Patient data were censored on termination of insurance coverage or at the end of the study period.

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Results: Overall, 7527 patients were prescribed a prostaglandin analogue; 4356 patients met the inclusion criteria (n = 2376, 993, and 987 for latanoprost, bimatoprost, and travoprost, respectively). A total of 58% of patients were women, and 74% were 65 years of age or older. Compared with latanoprost, those treated with bimatoprost were 38% more likely to discontinue and 31% more likely to discontinue/change therapy, and patients treated with travoprost were 36% more likely to discontinue and 29% more likely to discontinue/change therapy ($P < 0.001$ for each comparison).

Conclusion: Latanoprost-treated patients demonstrated significantly ($P < 0.001$) greater persistency than did those treated with either bimatoprost or travoprost. (*Clin. Ther.* 2003;25:1172–1185)

Key words: bimatoprost, glaucoma, latanoprost, ocular hypertension, persistency, travoprost.

INTRODUCTION

Open-angle glaucoma affects an estimated 33 million individuals worldwide.[1] In addition to increasing age and a family history of the condition, a major risk factor for open-angle glaucoma is an elevated intraocular pressure (IOP), although an elevated IOP is not necessary to the development of glaucoma and the causes of open-angle glaucoma remain to be clarified.[2] An IOP >21 mm Hg in individuals with no evidence of optic nerve damage is termed *ocular hypertension,* which has been estimated to affect as many as 10% of individuals 40 years of age or older.[2] Treatment of patients with open-angle glaucoma or ocular hypertension focuses on lowering IOP levels because such reductions slow disease progression in patients with glaucoma[3–5] and delay or prevent the progression of ocular hypertension to glaucoma.[6]

Although physicians traditionally have prescribed beta-blockers as first-line ocular hypotensive therapy, preferred pharmacotherapeutic options currently include prostaglandin analogues, alpha$_2$-adrenergic agonists, and carbonic anhydrase inhibitors.[7] Topical prostaglandins such as latanoprost (approved by the US Food and Drug Administration in 1996) and bimatoprost and travoprost (both approved in 2001), which lower IOP levels primarily by increasing uveoscleral outflow,[8,9] effectively reduce IOP levels.[10–14] The 3 prostaglandins are similar in that they require once-daily instillation and produce few systemic side effects.[10–14] Some prostaglandin-treated patients, however, experience *ocular hyperemia,* the reddening of the conjunctiva resulting from vasodilation.[8] Based on results of controlled clinical trials, hyperemia rates range from 5% to 15% for latanoprost,[15] 15% to 45% for bimatoprost,[16] and 35% to 50% for travoprost.[17] This condition is of concern because local and systemic side effects may nega-

tively affect whether the patient takes the drug as directed (*compliance*) and/or continues to use the drug over time (*persistency*).[18]

In routine practice, no ocular hypotensive therapy can provide IOP control unless the patient continues to use the drug over time. Persistency can be viewed as a surrogate marker for effectiveness (ie, IOP control), tolerability,[19] and costs.[20] Discontinuation of therapy constrains physicians' efforts to manage glaucoma and ocular hypertension. Similarly, when pharmacotherapy must be changed because a patient fails to achieve the target reduction in IOP, the change interrupts IOP control and may increase health care costs. In particular, such changes have been associated with more intensive monitoring and testing and, in some instances, surgery, all of which increase medical costs.[21,22]

To assess the outcomes of a disease, researchers and clinicians often use natural history cohort studies and analyze findings using survival analyses.[23] The same methodologies can be applied to studies of drug persistency. These rigorous approaches provide greater validity than simpler assessments of clinical events or outcomes because they adjust for limits on the length of the observed study period and also account for the loss of patients over time due to the occurrence either of the clinical event being studied or of "censoring" events (eg, leaving the health insurance plan or reaching the end of the study period) that prevent the clinical outcome from being observed. Clinicians and other health care decision makers can use such refined statistics to improve disease management.[23] The purpose of the present research was to use these techniques to assess persistency with prostaglandin analogues—latanoprost, bimatoprost, and travoprost—in the treatment of glaucoma or ocular hypertension.

MATERIALS AND METHODS

This was a population-based, retrospective cohort study. We used claims records from the Protocare Sciences managed care database, a national US database that includes ~3 million members each year with membership in commercial health maintenance organizations, preferred provider organization plans, and Medicare-risk plans. Information included in the database qualifies as "de-identified" data within the meaning of the safe-harbor privacy provisions promulgated by the Department of Health and Human Services, pursuant to the Health Insurance Portability and Accountability Act (HIPAA). In compliance with HIPAA regulations, the managed care organization database houses encrypted patient and provider identifiers as well as modified age and zip code formats and meets all other federal requirements for de-identified data.

Included in the initial population were patients 20 years of age or older who began therapy between April 2001 and June 2002 with either latanoprost, bimatoprost, or travoprost (*index drugs*). Patients were excluded from further analyses if, on the initial dispensing date (*index date*), they had not been continuously

enrolled in the insurance plan for the preceding 180 days, had received a prescription for any prostaglandin analogue in the preceding 180 days, were <20 years of age, or had received prescriptions for >1 ocular prostaglandin analogue. Patients who had received therapy with a nonprostaglandin glaucoma agent (eg, timolol or betaxolol) within the 180 days prior to the index date were included. Follow-up continued through June 30, 2002, and prescription refill records for all ocular hypotensive agents were extracted during this period.

Patients were identified as having *discontinued therapy* if they had no further index drug refills either 90 days (if dispensed 1 bottle) or 180 days (if dispensed >1 bottle) after the last prescription fill or refill (*discontinuation date*). These time frames were chosen because separate analyses (unpublished data, Informagenics, LLC, 2002) conducted using the same database indicated that most patients dispensed 1 bottle of a prostaglandin analogue refill their prescription within 40 to 60 days (mean, 43–62 days for the first 4 refills of the 2.5-mL size of the 3 index drugs); the 90-day interval between refills, therefore, allowed for some variation in prescription dosing and for noncompliance (eg, every-other-day use or skipping doses). Days of therapy on the index drug before discontinuation were calculated as the discontinuation date minus the index date. Patients were identified as having *changed therapy* if they switched to or added any ocular hypotensive medication other than a drug that they had received during the 180 days preceding the index date. Days of therapy on the index drug before changing were calculated as the change date minus the index date. Drug persistency was calculated as the time from the index date to: (1) the discontinuation date (*discontinuation event*); and (2) to the earlier of either the discontinuation or change dates (*discontinuation/change event*).

Chi-square tests were used to assess differences in proportions of patients in the various treatment groups with respect to age, sex, initial diagnosis, and frequency of glaucoma-related visits. Base-case Cox regression models were constructed to compare rate ratios of discontinuation and discontinuation/change across treatment groups with latanoprost as the comparator. Survival function plots were constructed from the Cox model to provide visual comparisons among treatment groups of the likelihood of remaining persistent with the index drugs; these plots allow absolute risks to be identified for any time point during the study period. Although not all patients were followed up long enough to observe their drug discontinuation or change in the pharmacy database, drug persistency still could be assessed by treating their data as censored either on termination of insurance coverage or at the end of study period.[24]

The stability of the base-case models was tested in patients who had not received any topical ocular hypotensive therapy (either prostaglandin or nonprostaglandin) in the 180 days preceding the index date; the sensitivity of the models was assessed by varying the refill time frame (using 60 and 120 days or 120 and 180 days for 1

or 2 medication bottles, respectively, vs the 90 and 180 days used in the base-case models). In addition, Cox regression models were constructed using bimatoprost as the comparator to allow rate ratios for outcomes in bimatoprost- and travoprost-treated patients to be compared directly. All statistical analyses were performed using Statistical Package for Social Sciences version 11.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Overall, 7527 patients were prescribed either latanoprost, bimatoprost, or travoprost during the study period; 4356 patients met all additional inclusion criteria (Table I). Of those patients included in the final study sample, latanoprost was prescribed for 2376 (55%), bimatoprost for 993 (23%), and travoprost for 987 (23%). Demographic and ocular characteristics are summarized in Table II. A total of 58% of patients were women, and 74% were 65 years of age or older. Approximately two thirds (64%) of those for whom a diagnosis was recorded had primary open-angle glaucoma; a specific diagnosis was not available in the medical claims database for the 42% of patients with no glaucoma-related visit during the 180 days preceding the index date. Compared with the other treatment groups, patients receiving travoprost were more likely to be diagnosed with open-angle glaucoma and to have had >1 glaucoma-related visit in the 180 days before the index date.

Cox regression model statistics for discontinuation and discontinuation/change for the base-case models are shown in Table III. Patients treated with bimatoprost and travoprost were 38% and 36%, respectively ($P < 0.001$ for both), more likely

Table I. Application of inclusion and exclusion criteria to the patient population.*

Application of Inclusion and Exclusion Criteria	No. Excluded	No. Included
Population of patients prescribed a first prostaglandin analogue between April 1, 2001, and June 30, 2002, and not prescribed a prostaglandin analogue in the 180 days preceding the initial dispensing date (index date)	–	7527
Patient was prescribed multiple prostaglandin analogues on the index date	5	7522
Patient was <20 years of age on the index date	50	7472
Patient did not have continuous drug benefit enrollment for 180 days preceding the index date	3116	4356

*The analysis included patients taking a single prostaglandin analogue, and the index drug was identified by the first prostaglandin prescription fill. Cotherapy with nonprostaglandin glaucoma agents was allowed.

Table II. Patient demographic and ocular characteristics (N = 4356).* (Values are expressed as no. [%] of patients. Percentages may not add to 100% due to rounding.)

Characteristic	Latanoprost	Bimatoprost	Travoprost
Patients	2376 (55)	993 (23)	987 (23)
Age, y			
20–34	27 (1)	9 (1)	13 (1)
35–49	157 (7)	60 (6)	42 (4)
50–64	464 (20)	201 (20)	180 (18)
65–79	1206 (51)	495 (50)	546 (55)
>79	522 (22)	228 (23)	206 (21)
Sex			
Women	1389 (59)	562 (57)	556 (56)
Men	987 (42)	431 (43)	431 (44)
Type of glaucoma†			
Open angle	860 (36)	337 (34)	419 (43)
Borderline	250 (11)	94 (10)	110 (11)
Other	251 (11)	107 (11)	80 (8)
Not documented	1015 (43)	455 (46)	378 (38)
Number of glaucoma-related visits in the 180 days preceding index date†			
0	1015 (43)	455 (46)	378 (38)
1	574 (24)	196 (20)	191 (19)
>1	787 (33)	342 (34)	418 (42)

*Based on data from the medical claims database.
†$P \leq 0.001$ for differences between all treatment groups.

to discontinue the index drug than were those treated with latanoprost. However, patients treated with bimatoprost were not significantly more likely to discontinue therapy than those treated with travoprost. Figure 1 provides corresponding survival plots showing that latanoprost-treated patients demonstrated the greatest persistency with therapy over time. The curves are flat for the first 90 days because patients could not discontinue their therapy during that time. Compared with patients receiving latanoprost, those treated with bimatoprost or travoprost were 31% ($P < 0.001$) and 29% ($P < 0.001$) more likely to discontinue/change therapy, respectively. The likelihood of discontinuing/changing therapy was not significantly different between those treated with bimatoprost and travoprost. Figure 2 presents survival plots for discontinuing or changing therapy for the 3 prostaglandins; declines in these curves before 90 days reflect changes in initial therapy.

Table III. Relative discontinuation and discontinuation/change of prostaglandin therapies: base-case models.*

	Rate Ratio	95% CI	P
Discontinuation of therapy			
Latanoprost†	1.00		
Bimatoprost	1.38	1.24–1.53	<0.001
Travoprost	1.36	1.21–1.51	<0.001
Discontinuation of or change in therapy			
Latanoprost†	1.00		
Bimatoprost	1.31	1.19–1.44	<0.001
Travoprost	1.29	1.17–1.42	<0.001

*Hazard rate ratios and 95% CIs from Cox regression models.
†Reference group.

The relative relationships among prostaglandins demonstrated in these base-case models were stable in patients who had not received ocular hypotensive therapy in the 180 days before the index date (n = 2139) and were not sensitive to changes in assumptions concerning refill time frames for all patients (Figures 3 and 4).

DISCUSSION

In chronic diseases such as glaucoma, medications must be taken as directed (*compliance*) over the long term (*persistency*). Studies of patient compliance and persistency with medical therapies for glaucoma traditionally have been descriptive,[25,26] assessed total nonadherence,[27] measured number of days without therapy,[27,28] and/or reported medication possession ratios.[28] Regardless of the method used, however, compliance and persistency have been found to be poor. Among the studies that used the medication possession ratio or similar rigorous measures, a 1-year retrospective cohort study[28] of members of a health maintenance organization who were first-time users of topical ocular hypotensive drugs found that 24.7% of patients did not fill sufficient prescriptions to cover at least 80.0% of study days and that, on average, patients were without therapy for a mean (SD) 103.9 (70.0) days of the year.

Although the medication possession ratio is a methodologic advance compared with descriptive techniques, the validity of such ratios is constrained because the sample being assessed must be limited to those with a uniform follow-up period, and the resulting statistic cannot describe how persistency changes during follow-up.[23] Survival analysis, which has been used to assess medical outcomes for >40 years,[29] overcomes these difficulties and has the added benefit of allowing imbalances in baseline characteristics to be controlled statistically.[23] A search of

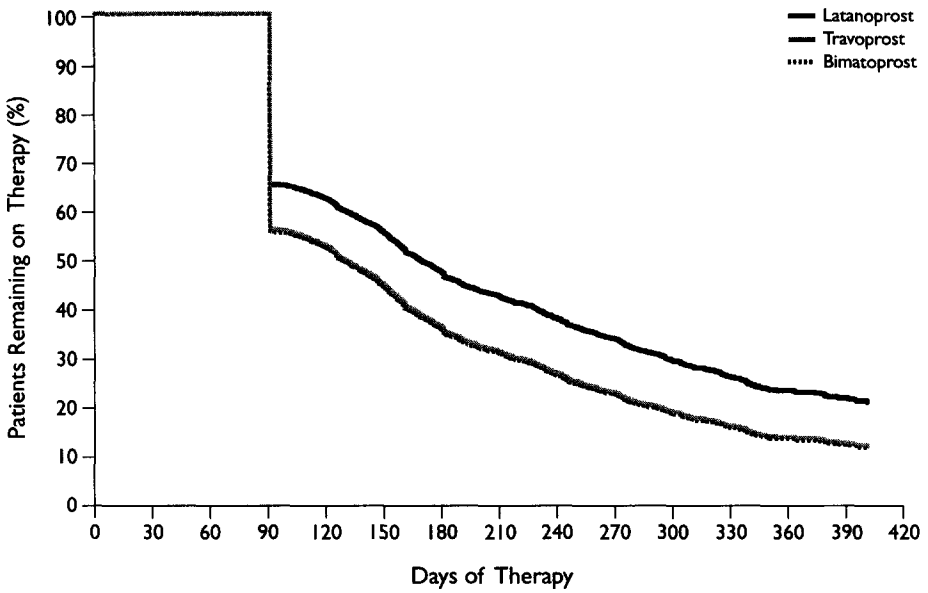

Figure 1. Plot of survival function for time to discontinuation of prostaglandin therapies.

MEDLINE using the PubMed search service and the key words *glaucoma, discontinuation, persistency,* and *survival analysis* showed that, during the past 10 years, the method was not applied widely in studies of persistency with ocular hypotensive drug therapy. Three retrospective cohort studies[19,30,31] published in 2002 used the technique to compare medication persistency over 18 to 30 months in patients treated with latanoprost versus beta-blockers, brimonidine, or carbonic anhydrase inhibitors. All 3 studies included >1000 patients <65 years of age who were members of managed care plans. Each found that patients treated initially with latanoprost monotherapy remained on therapy significantly ($P < 0.001$ to $P < 0.05$) longer than those treated with comparator drugs.

The present research assessed persistency among topical prostaglandins using survival analysis. In >4000 patients followed up for 15 months, those treated with latanoprost were found to be significantly ($P < 0.001$) more likely to continue therapy than patients receiving either bimatoprost or travoprost. Results were stable when models were tested in patients who had not recently been treated with any other ocular hypotensive and were not sensitive to changes in the duration allowed between refills. The retrospective, claims-based design of the present study cannot support an assessment of the reasons for increased persistency with

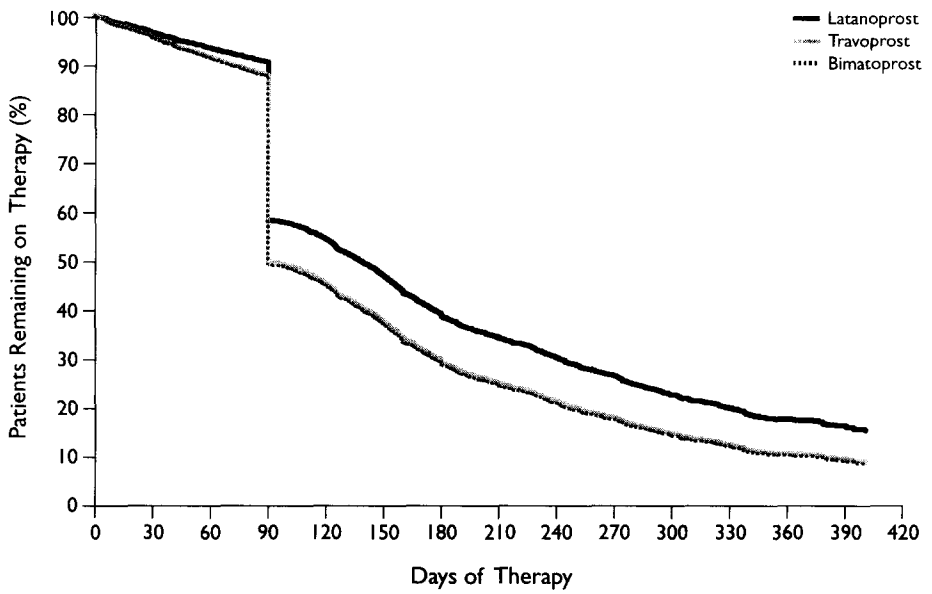

Figure 2. Plot of survival function for time to discontinuation of or change in prostaglandin therapies.

latanoprost. In general, however, variability in persistency primarily reflects differences among drugs in effectiveness, tolerability,[32] and costs.[20] As latanoprost, bimatoprost, and travoprost all have been shown to effectively reduce IOP levels[10–14] and their acquisition costs are similar,[33] differences in persistency may reflect variation among the 3 drugs with regard to tolerability.

Product labeling suggests wide variability with respect to the occurrence of hyperemia in patients using the 3 prostaglandin analogues,[15–17] and comparative clinical trials of pairs of drugs verify the magnitude and direction of these differences. In a 3-month study, Gandolfi et al[34] reported hyperemia rates of 14.2% in patients treated with latanoprost and 36.1% in bimatoprost-treated patients ($P \leq 0.001$). In addition, just 1.9% of those treated with latanoprost but 5.4% of patients treated with bimatoprost rated their hyperemia as more than mild. In a 6-month trial,[35] the hyperemia rate in those treated with latanoprost was less than half that in patients receiving bimatoprost (20.6% vs 44.4%, respectively; $P < 0.001$), and mean scores reflecting severity of hyperemia were significantly higher in bimatoprost-treated patients ($P < 0.001$). Hyperemia rates of 27.6% in latanoprost-treated patients, 38.0% in those treated with travoprost 0.0015%, and

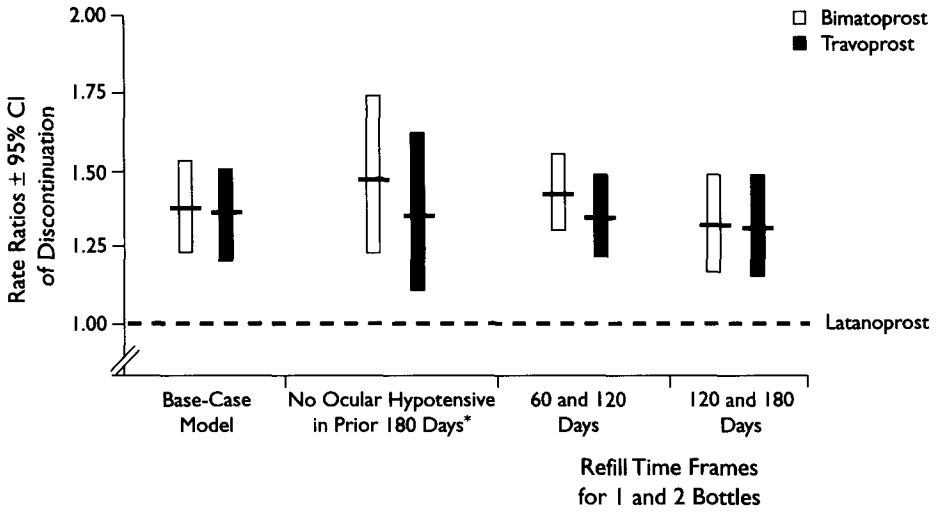

Figure 3. Rate ratios of discontinuation of prostaglandin therapies: stability and sensitivity analyses. *A total of 2139 patients had not received ocular hypotensive therapy in the 180 days preceding the index date.

49.5% in those receiving travoprost 0.004% were reported after a 12-month study[36]; the authors did not report tests of statistical significance. No direct comparison of such rates in patients treated with bimatoprost versus travoprost has been published.

The present study has both strengths and weaknesses. A strength of the electronic claims review method generally is its ability to include large numbers of patients, which provides the statistical power to detect differences among treatment groups. Assessing patients in an actual care setting rather than in a controlled experimental setting enhances generalizability by reducing biases introduced by the highly regimented therapeutic protocols used in clinical trials. Use of an actual care setting in the present study may explain the substantially higher discontinuation rates found for all 3 prostaglandins compared with the relatively low rates reported in controlled clinical trials.[10–14] Potential weaknesses of this study include the fact that incomplete records and/or physician dispensing of samples could have influenced results. Patients also were not required to have an *International Classification of Diseases, Ninth Revision*[37] diagnosis of glaucoma for inclusion, although previous research suggests that most patients who receive a prescription for a topical ocular hypotensive agent have a diagnosis of glaucoma or require IOP reduction.[38]

Although survival analysis provides a rigorous method for assessing relative differences in persistency among ocular hypotensive therapeutic options, we have found in similar unpublished work (unpublished data, Informagenics, LLC,

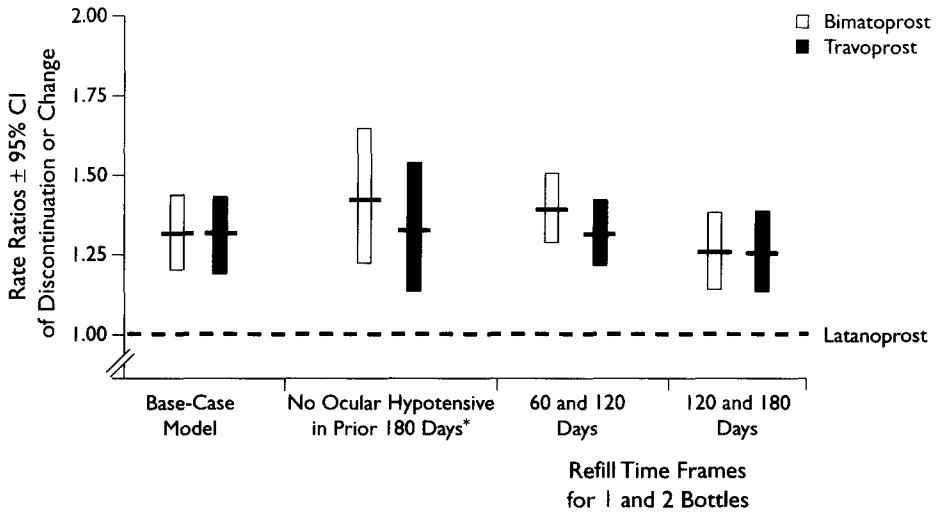

Figure 4. Rate ratios of discontinuation of or change in prostaglandin therapies: stability and sensitivity analyses. *A total of 2139 patients had not received ocular hypotensive therapy in the 180 days preceding the index date.

2002) that some patients return to therapy after a large gap between refills, and actual persistency rates over the long term may be considerably higher than those calculated here. Finally, researchers should continue to develop and refine methods to assess medication persistency. In particular, although the present study defined therapy change as either switching or adding any ocular hypotensive medication, researchers should test potential methods of distinguishing between patients who add versus switch therapies.

Once the efficacy and tolerability of a therapy have been assessed in controlled clinical trials, physicians begin to assess the drug's effectiveness and tolerability in routine practice settings. At that point, assessing persistency with therapy also becomes important because patients who do not fill their prescriptions do not receive adequate treatment, and over time, lack of persistency is equivalent to treatment withdrawal. In patients with glaucoma or ocular hypertension, such withdrawals may lead to elevated IOP levels and disease progression that can result in blindness.

CONCLUSIONS

Latanoprost-treated patients demonstrated at least 29% greater persistency than did those treated with either bimatoprost or travoprost. The reasons for such differences in persistency and the long-term impact of such variation on both IOP control and costs warrant further assessment.

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